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Effect of solvent and temperature on solution-crystallized terfenadine

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Abstract

The aim of this work was to understand the crystallization process of terfenadine in solution.

Cooling of saturated solutions prepared at 50 °C at different temperatures, evaporating the solvent from nearly saturated solutions at a certain temperature, and exposing ethanol solutions of terfenadine to water vapour atmosphere were the techniques used for obtaining terfenadine specimens. The characterization of these specimens was carried out by thermal microscopy, differential thermal analysis, thermogravimetry and powder X-ray diffraction. Crystalline phases, amorphous solids, and solvates were identified. For the solvents used in the present study, the crystallinity degree of terfenadine decreases from ethanol–water to ethanol and from this to methanol. Decreasing the temperature promotes the formation of amorphous solid material; at low temperatures, methanol and ethanol solvates are also formed.

Desolvation, following the terfenadine aggregation process in solution accounts for the different behaviour found for the solvents and for the effect of temperature on the structure. The role of the solvent as structure-mediator is explained on the grounds of the values previously published for the enthalpy of solution of terfenadine in the solvents under study.

Keywords: Terfenadine; Crystallization; Aggregation; Polymorphism

1. Introduction

Polymorphism became an emerging research field after discovering that structural modifications of organic medicinal compounds give rise to different properties such as bioavailability, morphology and stability [1,2]. Since then, the pharmaceutical industry carries out research on polymorphism of drugs in order to offer increasingly efficient medicines and to gain control over the preparation of solids with desired physical properties [3,4].

As solvents play an important role in the structure of solids in the crystallization process, this technique is a common way for preparing polymorphs [4]. However, it is not a straightforward method for getting single forms as, besides the stable solid compatible with the experimental conditions, often disordered material is precipitated from solvents jointly with crystalline state phase. This proves that crystallization in solution is a very complex process deserving much attention owing to its importance in crystal engineering [5,6].

Most of the work performed on the preparation of polymorphs by crystallization in solution is concerned with the characterization of the solid structures formed in a given solvent under specified conditions. To overstep such trial-and-error procedure, it is essential to establish guidelines leading to desired polymorphic forms. To reach this stage, we need to understand crystallization at molecular level of different types of solutes in different solvents under several experimental conditions.

Solution calorimetry is a privileged research method for understanding the crystallization in solution. Indeed, valuable information regarding the role played by the solvent and the molecular aggregation processes can be drawn from the enthalpy of solution at infinite dilution and from the variation of the enthalpy with the concentration. The former property is related with the solute solvation and the later with the interaction between the solute molecules from monomers to the solidification critical nucleus.

As embryo of the emergent new phase the structure of the nucleus is determinant of that of the solid.

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A rather comprehensive work on polymorphism of terfenadine was recently carried out by the authors of the present paper. Four polymorphs were defined in specimens prepared from ethanol, methanol and ethanol–water under different temperatures after being submitted to thermal curing at 100 °C [7].

The aim of the present work is the interpretation of the crystallization of terfenadine in different solvents and at different temperatures on the grounds of thermodynamic properties. The specimens obtained were characterized by hot-stage microscopy, differential thermal analysis, thermogravimetry and X-ray powder diffractometry and the results interpreted on physical chemical grounds.

Terfenadine, 1-(4-*tert*-butylphenyl)-4-[4′-(diphenyl-hydroxymethyl)-1′-piperidyl]butan-1-ol, is a non-sedating antihistamine drug compound included in the polymorphism research activity of our group [8,9].

Research in 1990s on polymorphism of terfenadine obtained from crystallization in solution led to conclusion that this compound in solid state can be present in two or three structural modification [10–15].

2. Materials and methods

2.1. Chemicals

Terfenadine commercialized by Sigma–Aldrich was the original material used for preparing the specimens under consideration. A preliminary differential scanning calorimetric test performed on the commercial product showed a single fusion peak characterized by $T_{onset} = 149.7 \pm 0.43$ °C, $T_{peak} = 150.4 \pm 0.30$ °C and width-half-maximum of 0.9 ± 0.02 °C. The comparison of these features with the data obtained for terfenadine in previous studies leads to the conclusion that the substance is a high melting polymorphic form [7].

Methanol and ethanol (Merck Uvasol grade) used as solvent were kept and handled with care in order to avoid contamination with water vapour during storage and experimental procedure.

2.2. Crystallization procedures

Supersaturation was generated by slow evaporation of the solvent from a saturated solution of terfenadine or by cooling, at different temperatures, a nearly saturated solution at 50 °C. Besides these techniques, terfenadine specimens were prepared by water vapour diffusion into an ethanol solution. An ethanol solution of terfenadine was maintained at 20 °C in a tightly closed vessel containing a 1:1 water–alcohol mixture. As the terfenadine is almost insoluble in water, the uptake of water vapour by the solution gives rise to the solid phase.

The methods used for preparing the specimens are summarized in Table 1. The solid was separated from the liquid, dried at 40 °C under vacuum for 48 h and kept in a desiccator.

Table 1
Methods used in the preparation of terfenadine crystallized from solution

Specimen[a]	Solvent	Method
E1	Ethanol	Solvent evaporation at 50 °C
E2	Ethanol	Solvent evaporation at 20 °C
E2′	Ethanol	Cooling at 20 °C
E3	Ethanol	Cooling at 3 °C
E4	Ethanol	Cooling at −5 °C
M1	Methanol	Solvent evaporation at 50 °C
M2	Methanol	Solvent evaporation at 20 °C
M2′	Methanol	Cooling at 20 °C
M3	Methanol	Cooling at 3 °C
M4	Methanol	Cooling at −5 °C
E–W3	Ethanol:water (4:1, v/v)	Cooling at 20 °C
E–Wv	Ethanol:water (1:1, v/v)	Vapour diffusion at 20 °C

[a] Capital letters stand for solvent and numbers denote the temperature at which crystallization was undertaken. The prime is used when two specimens were prepared at the same temperature.

2.3. Instruments

Hot-stage, Mettler FP84HT TA, connected to FP900 control unit was the thermal equipment used in thermomicroscopy. This equipment allows the recording of DTA curves during thermal cycles simultaneously with microscopic observation.

Temperature readings of the control unit were checked by determining the melting point of benzophenone (Mettler Toledo Calibration Substance ME 18′870, $T_{fus} = 48.1 \pm 0.2$ °C) and benzoic acid (Mettler Toledo Calibration Substance ME 18′555, $T_{fus} = 122.3 \pm 0.2$ °C). The readings obtained for these standards were 48.1 ± 0.2 and 122.4 ± 0.2 °C, respectively.

The optical equipment attached to the hot-stage system consists of a DMRB Leica microscope equipped with polarized light facilities, to which a Sony image processing assembly composed of a CCD video camera (Sony DXC-151 AP), video tape recorder (Sony SVO-1500P VHS VCR), colour video monitor (Sony PVM-2053 MD) and colour video printer (Sony UP-1200 RP) were attached. A digital video capturing equipment on computer, Studio DC10 Plus from Pinacle Systems, was used for editing the image. Image frame grabber permitted collection of individual images to give details of particular aspects to be studied.

The thermal program for the microscopic examination was run at heating rates between 10 and 1 °C/min. The samples under observation were dispersed in an open 7 mm quartz crucible.

Thermogravimetric analysis was performed with a Rheometric Scientific STA 1500 apparatus. Temperature calibration was carried out using the values tabled for indium, tin and lead. The heating run selected was 10 °C/min and the purge was achieved by a 50 ml min^{-1} flow of dry nitrogen.

A X-ray diffractometer (Philips 1830) was employed for recording the X-ray pattern of the samples under study. The powder diffraction spectra were obtained with a Cu $K\alpha_1$ source operating at a tube load of 40 kV and 30 mA. Powder samples of particle size below 300 μm were packed onto 16 mm diameter stainless steel holder and gently pressed. Scans were accumulated over the range of 3–40° (2θ) with a step size of 0.02° (2θ) and the collection time of 1 h. Counting was detected with a time constant of 1.25 s.

3. Characterization of terfenadine

3.1. Thermomicroscopy

Crystalline phases, amorphous solid material, and solvates may be observed by thermal microscopy. Most specimens show the presence of more than one of this kind of structure. According to the phases present, the specimens can be included into three groups. One, denominated group I, includes specimens which, under polarized light observation

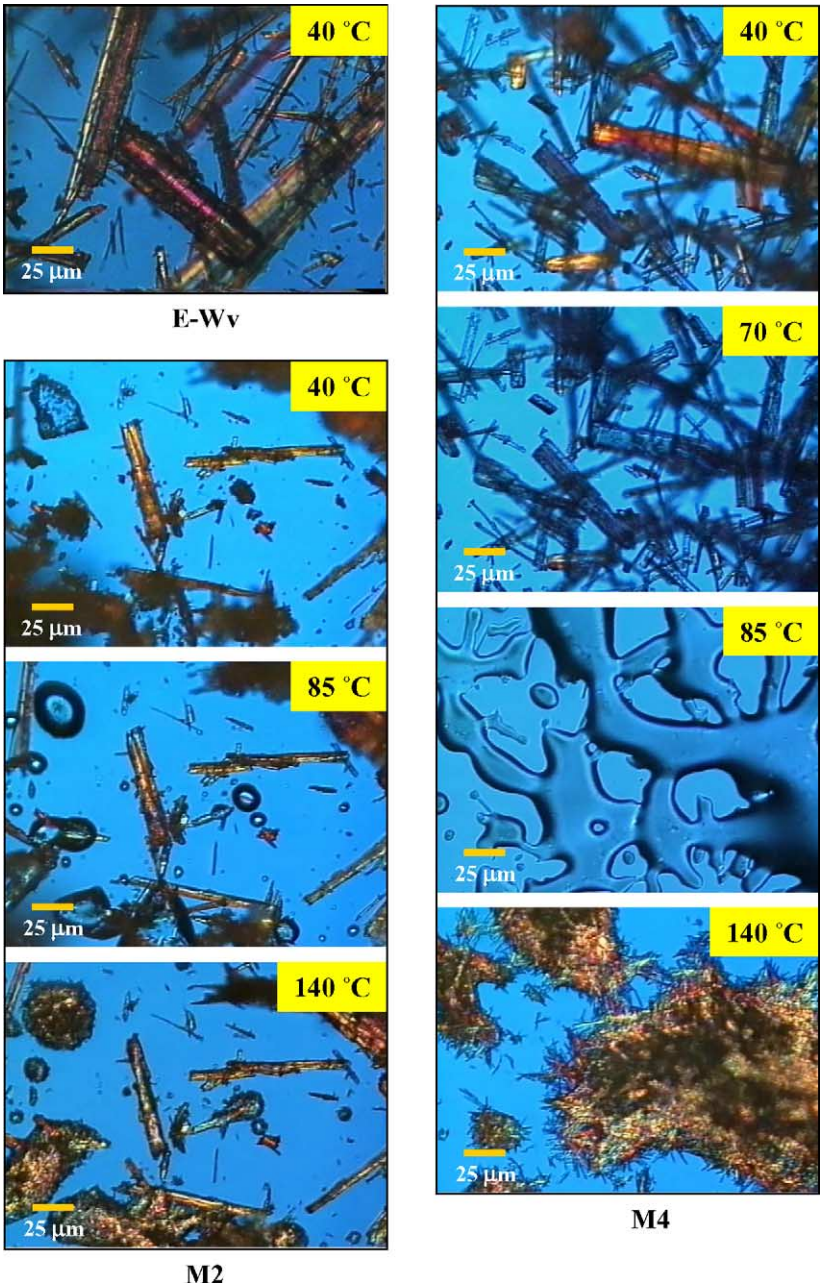

Fig. 1. Micrographs showing the solid state forms of terfenadine obtained by crystallization from solvents and the transformations observed by heating. E–Wv, typical image of crystalline solid (type I). M2, phase transition in a type II specimen—40 °C, crystalline phase and amorphous material; 85 °C, primitive crystalline phase and liquid; 140 °C, primitive and crystalline phase proceeding from molten. M4, phase transition in a type III specimen—40 °C, methanol solvate; 70 °C, desolvated methanol solvate; 85 °C, molten solvate; 140 °C, crystalline solid phase arisen from the molten.

shows elongated crystalline thermally stable aggregates; another group, denoted by group II, is characterized by crystalline aggregates like those observed for I, and by particles of irregular shape and various sizes which do not exhibit light birefringence; that is, this group is characterized by the coexistence of crystalline and amorphous phases. Finally, group III, consists mainly of amorphous solid, and ethanol or methanol–solvate which appears as a low melting crystalline phase. Small crystalline aggregates of the higher melting crystalline phase are also observed in the specimens included in this group. Terfenadine specimens labelled as E1, E2, E2′, M1, E–W3 and E–Wv belong to the first group (I). Those numbered as E3, M2 and M2′ are included in the second (II) and E4, M3 and M4 are part of the third (III).

The microscopic observation of the samples submitted to heating and cooling thermal runs gives valuable information on their structures. Type I specimens do not show any phase transformation when submitted to a heating run, but fusion which takes place in 147–150 °C temperature range. The melt gives rise on cooling to a glassy state as the temperature reaches a value around 50 °C. No crystallization of the glass is observed for years at room temperature.

On heating a group II specimen at 75 °C the amorphous material becomes liquid; the supercooled liquid remains stable for hours if temperature does not exceed 80 °C, but on further heating a slow crystallization process takes place in the temperature interval between 90 and 120 °C. The final solid phase has a melting point in the same range of temperature as the specimens of the group I.

The specimens of group III exhibit still a more complex pattern than that described for II. First, the transformation of the solvate into amorphous state is observed just before fusion. Although these two transitions take place in a narrow temperature interval, they can be well followed through microscopy. Similarly to what happens with II specimens, the supercooled liquid resulting from the amorphous solid material recrystallizes. Regarding crystallization of the supercooled liquid on heating, a difference between groups II and III is observed. In fact, for group II specimens the crystallization is initiated at a lower temperature and is faster than for group III. These differences may be understood on the grounds of the composition. Whilst in group II the liquid is in contact with the surface of a crystalline phase which may act as nucleation sites, in group III the liquid is almost a homogeneous system requiring higher energy for nucleus formation [16,17].

The images presented in Fig. 1 illustrate the different phases of terfenadine obtained from solvents and the transitions in which they are involved during the heating process.

3.2. Differential thermal analysis

Differential thermal analysis curves following the heating process performed on the specimens under consideration from 20 °C to fusion at a heating rate of 10 °C/min are illustrated in Fig. 2. The three types of terfenadine obtained from solution and described before can be characterized by these curves. Type I specimens show only one endothermic transition which corresponds to the fusion of the crystalline phases formed in solution. As expected from the thermomicroscopic observations, the group II specimens show two endothermic and one exothermic transitions. As the temperature increases, the first endotherm regards the melting of the amorphous solid, the exotherm, the crystallization of the resulting liquid; and the second endotherm, the melting of the phases originated from solution and from the amorphous solid transformation. The pattern shown by group III specimens is apparently identical to that of group II. However, two differences should be pointed out. First, the lower temperature endotherm obtained for group III is a composed curve which can be deconvoluted into two curves whose maxima are at 63 and 70 °C. As explained before, the two overlapped curves correspond to the transformation of the solvate into amorphous (*vide* Fig. 3) and to the melting of this solid form. Second, the exotherm of group III occurs at a higher temperature and is wider than that obtained for group II.

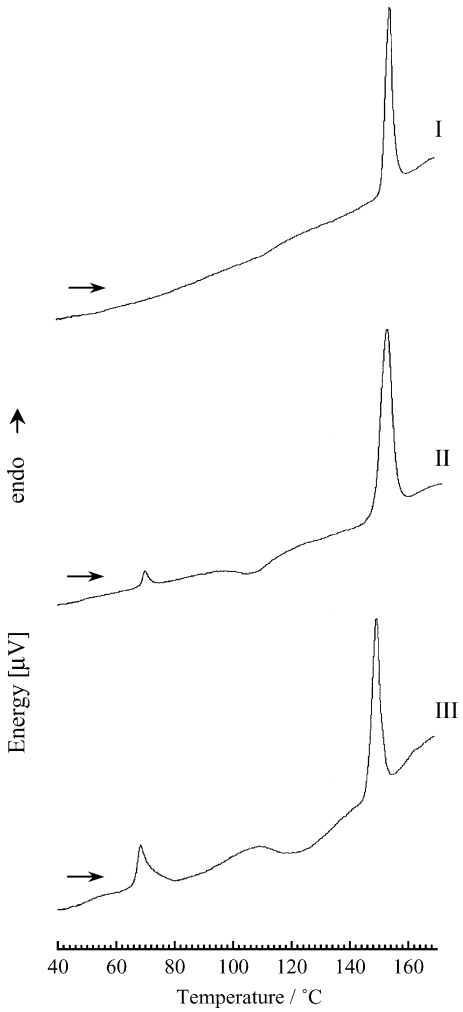

Fig. 2. DTA curves shown by terfenadine crystallized from solution. I, II and III are typical curves observed for the respective groups of solid material described in the text.

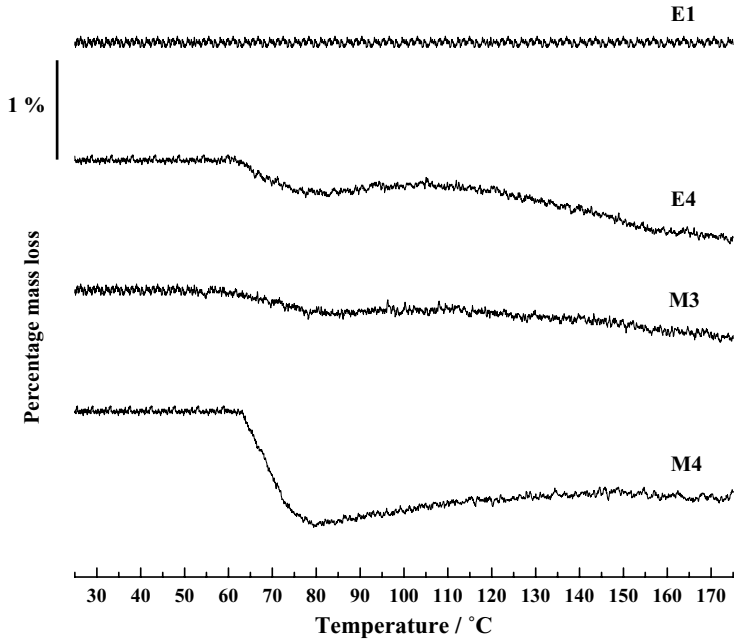

Fig. 3. TG patterns shown by terfenadine obtained from crystallization. The behavior of sample E1 is observed for all solids of group I or II. E4, M3, and M4 are the patterns for the solids included in group III.

3.3. X-ray diffraction

X-ray diffraction studies on terfenadine, as far as we know were only published by Blanchard [18] and by Hakanen and Laine [14]. The former author did not mention the existence of polymorphic forms whilst the authors of the second paper give powder diffraction patterns for a high melting and a low melting polymorph as well as for a methanol solvate. The high melting form was prepared from ethanol, the low melting one from acetone, and the solvate, from methanol. The data published by Blanchard [18] are found in the International Center of Diffraction Data under "i" mark classification and differ from all of those given by Hakanen and Laine [14]. Therefore at this stage no reference is available for the identification of terfenadine forms by X-ray diffraction, neither do we have methods for the preparation of single well-defined polymorphs. Despite these gaps, X-ray diffraction data are useful for determining the degree of crystallinity of the specimens under consideration and for comparing their structures.

The specimens included in group I are composed of crystalline phases. However, significant differences for the relative intensity and for the peak positions are observed between them. One type of pattern is observed for the specimens prepared from ethanol (E1, E2, E2′, E3), another is exhibited by the specimen prepared from methanol at 50 °C (M1) and a third one characterizes the specimens obtained from ethanol–water (E–W3 and E–Wv). The three types of X-ray powder diffraction patterns are presented in Fig. 4.

Regarding the diffraction pictures obtained for the crystalline phases, we can not ascribe the differences between them as being distinct polymorphic forms. Instead these dif-

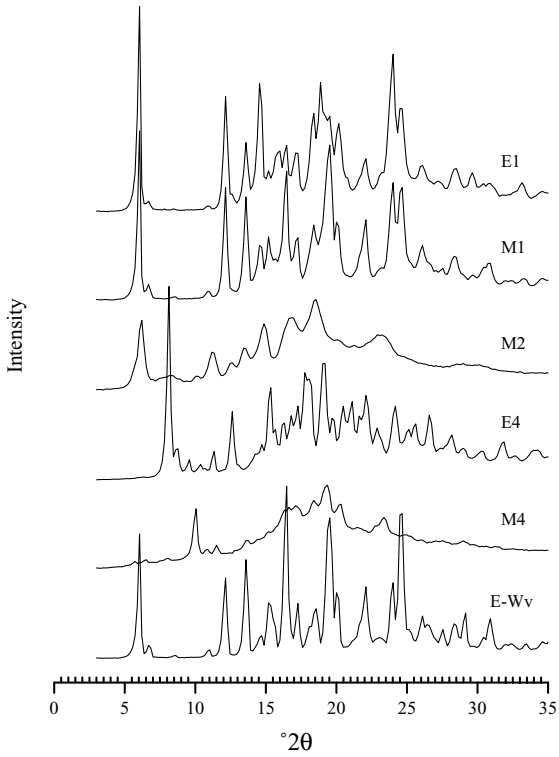

Fig. 4. X-ray powder diffraction patterns of terfenadine grown in solution illustrating the presence of crystalline, amorphous and solvate states. E1 and M1, crystalline solid phases; M2, crystalline and amorphous solid phases; E4 and M4, ethanol and methanol solvates. E–Wv, crystalline single phase.

ferences may be due to mixtures of single solid phases. Indeed the existence of concomitant polymorphs has been reported for some systems [19]. Some more elements are needed in order to decide whether the structures illustrated by E1 and M1 are single or crystalline mixtures. The elements we have on the E–Wv specimen, lead to the conclusion that it is a single polymorphic form [7].

The group of specimens denoted as II, due to the presence of amorphous solid phase shows broad diffraction peaks as observed for M2. The specimens of group III show broad diffraction peaks due to the presence of amorphous solid material and characteristic peaks of the solvates. The characteristic line for the ethanol solvate is observed at 8.250° (2θ) and that for the methanol solvate at 10.165° (2θ).

Besides the evidence for crystalline, amorphous and solvate states of terfenadine, X-ray diffraction points out the existence of different polymorphs of this substance generated in solution.

4. Discussion

Crystalline, amorphous and solvates are solid phases obtained in the crystallization of terfenadine using the procedures described above. The nature of the solvent and the temperature at which crystallization takes place play a role in the structure of the solid state obtained. The increase of the temperature tends to originate crystalline forms whereas its decrease tends to give rise to amorphous and solvates. The comparison of ethanol with methanol as solvent, at the same temperature, gives evidence of the higher degree of crystallinity of terfenadine precipitated from the former solvent relatively to the later. Ethanol–water at room temperature gives crystalline phases, whether the solidification is by cooling or by vapour diffusion technique.

A deep insight into the crystallization process can be reached by calorimetry. Indeed, the enthalpy of transferring the solute molecule from the normal state of aggregation to an infinite dilute solution, $\Delta_{sol}H^{\circ}$, provides valuable information about solute–solvent intermolecular forces. The variation of $\Delta_{sol}H$ with concentration is also a useful quantity for following the formation of the solid phase from solution. Data for these thermodynamic quantities for terfenadine in ethanol, methanol and ethanol–water at 25 °C were given in previous publications [20,21]. Thus, in the foregoing discussion, we will refer the data quoted for these properties which are inserted in Table 2. In the same table are displayed the approximate values determined for the variation of $\Delta_{sol}H$ from a high-dilute to a saturated solution, $\Delta(\Delta_{sol}H)$.

As shown in Table 2, the dissolution of crystalline terfenadine in any of the solvents we are dealing with is an endothermic process. A positive value found for $\Delta_{sol}H^{\circ}$ means that the dissolution is accompanied not only by an increase of the enthalpy but also by an increase of entropy, so that the entropic term of Gibbs energy overcomes the enthalpic one. Based on the values of $\Delta_{sol}H^{\circ}$ observed for the different solvents, we conclude that solute–solvent interaction increases from ethanol–water to ethanol and from this to methanol. This order was expected from the characteristic properties of the liquids towards the solute structure. The terfenadine molecule has three polar centres (the hydroxylic groups and the nitrogen atom) and a large nonpolar part. It can interact with dipolar protic solvents, as those we are considering, mainly by hydrogen bonding involving solute and solvent polar parts and by dispersion forces involving nonpolar ones.

Table 2
Limit value of the enthalpy of solution of terfenadine in different solvents, $\Delta_{sol}H^{\circ}$, and the variation of the enthalpy of solution from a dilute to a saturated solution [20,21], $\Delta(\Delta_{sol}H)$

Solvent	$\Delta_{sol}H^{o}$ (kJ mol^{-1})	$\Delta(\Delta_{sol}H)$ (kJ mol^{-1})
Methanol	19.8 ± 0.13	1.9 ± 0.13
Ethanol	21.1 ± 0.28	0.8 ± 0.28
Ethanol:water (85:15, v/v)	24.6 ± 0.03	1.6 ± 0.06

Temperature 25 °C.

The higher dipole moment of methanol relatively to that of ethanol and the higher molecular polarizability of the latter alcohol relatively to the former leads to the conclusion that the interactions between solute and solvent polar sites are stronger with methanol than with ethanol. On the contrary we expect that ethanol favours the interaction between the nonpolar moieties of the solute and the solvent relatively to methanol. The same conclusions are reached on the grounds of the values tabled for the polarity index and hydrogen bond donation or acceptance ability for these alcohols [22]. The molecular interaction between ethanol and water weakens solute–solvent forces between co-solvent and terfenadine. Indeed the effect of water on the decrease of solute–solvent interaction can be seen in the solubility of the terfenadine. The solubility of this substance in pure ethanol at 298.15 K is 0.071 ± 0.0017 M whereas in ethanol–water (85:15, v/v) at the same temperature it is 0.0221±0.00026 M [23]. Spectroscopic data on alcohol rich solutions give evidence of an ethanol–water interaction stronger than that of ethanol–ethanol [24].

In short, from the values of $\Delta_{sol}H^{\circ}$ quoted for terfenadine in the solvents employed in the crystallization of this substance, one can say that solvation is dominated by the interaction of the solvent with the solute polar centres and that this interaction decreases from methanol to ethanol and to ethanol–water.

The variation of the enthalpy of solution with the concentration, giving information on solute–solute interaction, is valuable for following the crystallization process in solution. As can be seen in Fig. 1 of the paper by Canotilho et al. [20], for all solvents, $\Delta_{sol}H$ is positive and increases as temperature increases. Rather different patterns of $\Delta_{sol}H$ versus molality curves are shown by ethanol relatively to methanol and ethanol–water mixture. Whilst in ethanol the increasing of $\Delta_{sol}H$ is almost gradual, for the other media

those curves exhibit a sudden increase as the concentration reaches a value around 0.01 M. Very likely in ethanol the terfenadine molecules are being incorporated in growing *n*-mer aggregates. In the other solvents, a weak molecular association occurs till the concentration reaches critical value and an aggregate is then formed by an assortment of *n* solute molecules.

Whatever the mechanism, on the thermodynamic point of view, for all systems the enthalpy of solution is positive and increases as the concentration increases. This means that the molecular association of terfenadine in solution is an endothermic and entropy driven process.

The assembling of a certain number of terfenadine molecules to form the solid phase embryo can be schematically expressed by the following reaction

$$n(A : xS) \rightarrow A_n : yS + (nx - y)S$$

A stands for terfenadine, *S* for solvent, *x* and *y* are the number of solvent molecules involved in the monomer and in the *n*-mer aggregate.

For the sake of simplifying the thermodynamic interpretation, we can consider the global aggregation process of the terfenadine in solution as composed of the following three steps: desolvation of the monomeric terfenadine molecule, self-assembling of desolvated terfenadine in *n*-mers aggregates, aggregate–solvent interaction. The association of desolvated terfenadine molecules as the result of the forces set up between the solute molecules is enthalpy favourable and entropy unfavourable. On the other hand, desolvation–solvation will give a positive contribution to the enthalpy and to the entropy because the number of solvent molecules taking part in the monomer solvation co-sphere affected by the molecular association is higher than those attached to the aggregate. The positive values obtained for $\Delta(\Delta_{sol}H)$ means that the contribution to the thermodynamic properties coming from the steps involving the solvent overcomes that owing to the interaction between terfenadine molecules themselves; the solvent plays a key role in the molecular aggregation. As a critical size is reached, the terfenadine aggregates become nuclei of the solid phase. Thence, the structure of this phase will depend much on the structure of the aggregates.

Although the investigation of the molecular structure is out of the scope of thermodynamics, some information can be drawn from the solvation data presented above and from the nature of the solids obtained from the solvents used in crystallization. In fact, taking into account that increasing temperature or decreasing solvent polarity improve terfenadine crystallinity, one concludes that crystalline state is formed in conditions favouring the desolvation of the terfenadine as self-assembling takes place. Thence we can infer that the nucleus originating the solid phase is composed of unsolvated terfenadine molecules. Among the systems under study this happens with ethanol–water and ethanol specially at temperatures above 3 °C. At lower temperatures or in the presence of solvents more strongly bonded to the polar centres of the solute, the aggregate is formed by solvated terfenadine molecules. The interaction between the polar centres of the solute blocked by the solvent is not relevant, resulting in a poorly ordered aggregate. Very likely this is what happens with ethanol at 3 °C and methanol between 50 and 3 °C. At an even lower temperature a stronger interaction between terfenadine and the solvent leads to its incorporation in a crystalline solid structure giving rise to solvates. As expected from the solute–solvent interaction, these pseudopolymorphs are easier to get from methanol than from ethanol. This is what happens with ethanol below 3 °C and methanol below 50 °C.

5. Conclusions

The systematic study on the crystallization of terfenadine under different solvents and experimental conditions lead to conclusions valid either for this compound or for other organic compounds.

The structure of terfenadine in the solid state, like many other organic crystal, is defined mainly by the hydrogen bonds established between the molecular polar centres. Thus, the results observed for terfenadine are valuable informations for predicting crystallization outcomes of other compounds, in particular, those containing nitrogen and hydroxyl as polar groups. Many organic compounds of biological interest have this type of groups.

Liquids as similar as ethanol and methanol under identical conditions give rise to terfenadine specimens of different crystallinity degrees. Ethanol favours a higher crystalline solid relatively to methanol. Temperature at which crystallization is performed is a determinant factor on the structure of the generated solid state. The crystalline state is favoured by increasing the temperature. As temperature decreases the amount of precipitated disordered material increases and at lower temperatures formation of solvates take place.

These findings are explained on the grounds of the competition between solute/solvent and solute/solute interactions as evidenced by solution thermodynamic properties.

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